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Danazol Therapy in Cyclic Acquired Amegakaryocytic Thrombocytopenic Purpura: A Case Report

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Cyclic acquired amegakaryocytic thrombocytopenic purpura (AATP) is a rare disorder characterized by periodic fluctuations in the platelet counts due to a defect in the platelet production. We describe a 42-year-old female with cyclic AATP, in whom the cyclic fluctuations in the platelet counts ceased with danazol therapy. The pathogenesis of the disease and the possible mechanisms of danazol action have been reviewed. Am. J. Hematol. 60:225–228, 1999. © 1999 Wiley-Liss, Inc.

Key words: cyclic amegakaryocytic thrombocytopenic purpura; danazol

INTRODUCTION

Cyclic thrombocytopenia is a rare disorder characterized by regular periodic fluctuations in the platelet counts,varying from severe thrombocytopenia to normal or increased platelet counts. The fluctuations in the platelet counts can be secondary to defective platelet production (amegakaryocytic type) or increased destruction of the platelets by the reticulo-endothelial system (the megakaryocytic variety). Amegakaryocytic cyclic thrombocytopenia (cyclic AATP) is rare; seven cases have been reported in males and only three cases in females [1–10].

We describe a premenopausal female with cyclic AATP who was successfully treated with danazol. The possible pathogenesis of the disease and the mechanisms of danazol action are discussed.

CASE REPORT

A 42-year-old premenopausal female presented with history of bleeding gums, petechiae, ecchymosis, and menorrhagia of two months' duration, in June 1993. The physical examination revealed petechiae and ecchymosis over the limbs and the trunk. The systemic examination was normal. The preliminary investigations revealed hemoglobin (Hb) 138 gm/l, total leukocyte count 10.2 × 10^9/l, and platelet count 50 × 10^9/l. Bone marrow aspirate was dilute, the erythroid and myeloid series showed normoblastic maturation and there was absence of megakaryocytes. The patient was treated with intravenous immunoglobulin (400 mg/kg/d × 5 days) with a provisional diagnosis of immune thrombocytopenic purpura. She had an apparent clinical improvement with a rise in the platelet count to 100 × 10^9/l over the next 8 days and it further rose to 220 × 10^9/l by the 15th day. The patient became symptomatic again after one month and presented with bleeding gums and menorrhagia, and the platelet count was 40 × 10^9/l. Splenectomy was performed, following which the platelet count rose to 340 × 10^9/l. However, the patient did not have a sustained remission and during the follow-up period she was observed to have similar symptoms in a cyclic pattern. The platelet counts varied between 30 × 10^9/l to 600 × 10^9/l during each cycle and the duration of each cycle varied between 20–28 days. The leukocyte and/or the reticulocyte did not show any cyclic variation. During this period she was admitted twice for the management of her bleeding episodes. Infusion of fresh plasma (FFP) obtained from a normal donor had no effect on her platelet counts and she was managed with supportive care (Fig. 1). A bone marrow biopsy performed during the thrombocytopenic phase showed complete absence of megakaryocytes with normoblastic erythropoiesis and granulopoiesis (Fig. 2). A second bone marrow examination done during the phase of thrombocytosis revealed an increased

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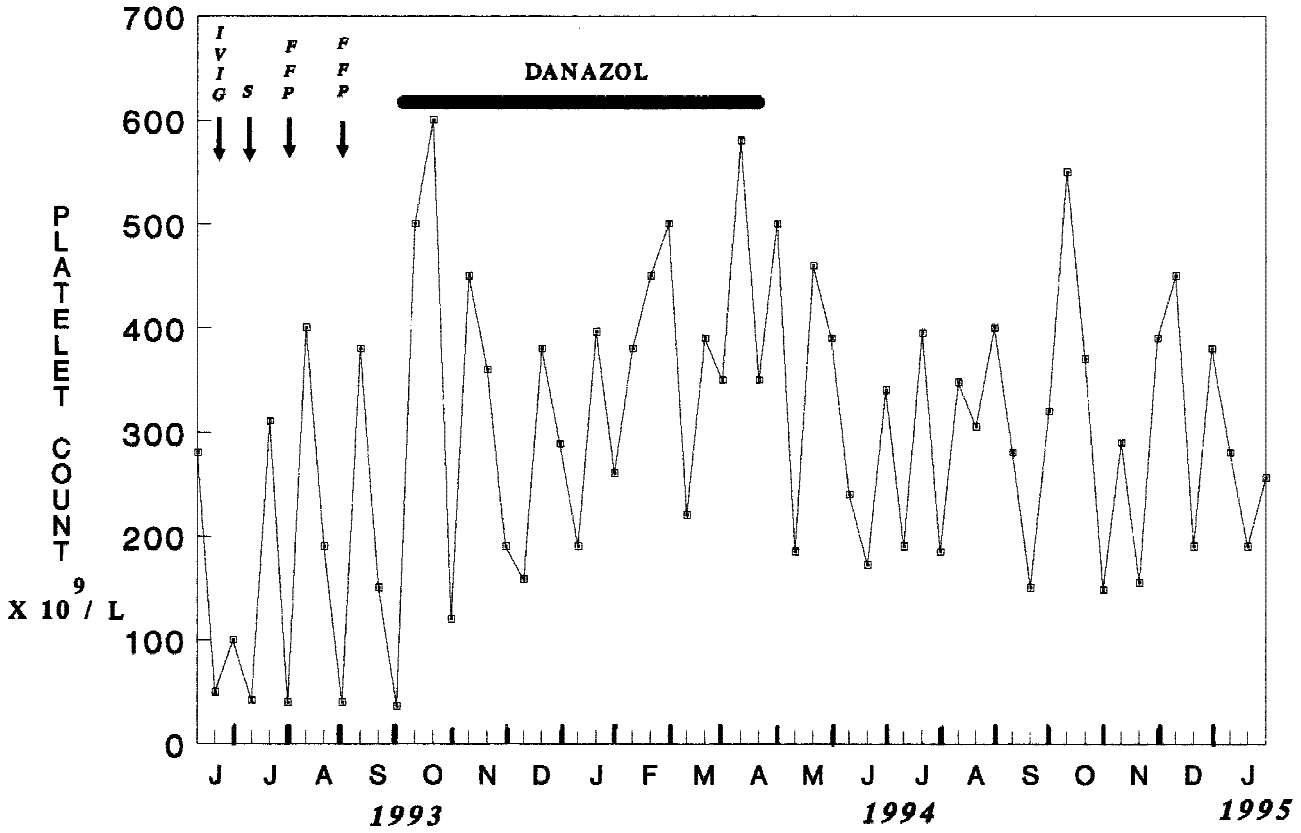

Fig. 1. Clinical course of the patient shows cyclic fluctuations of the platelet count and response to danazol therapy. On danazol treatment, the variation in platelet count decreased with less severe nadirs of thrombocytopenia and the patient was symptom free. Danazol was discontinued after six months and the platelet counts remained within the normal range for the remaining follow-up period. Abbreviations: IVIG, intravenous immunoglobulin; S, splenectomy, FFP, fresh frozen plasma.

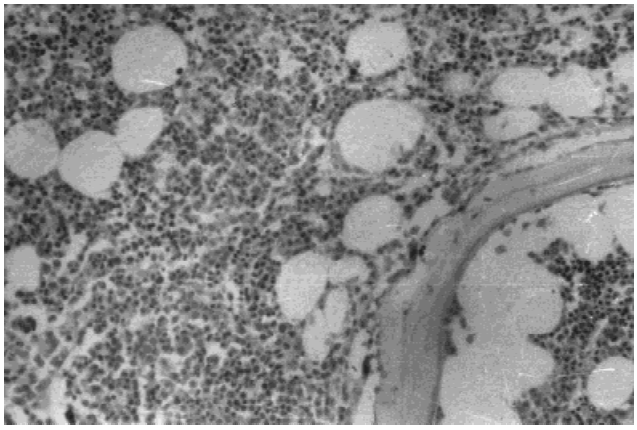

Fig. 2. Bone biopsy specimen performed during thrombocytopenia phase, shows near-total absence of megakaryocytes with normal erythroid and granulopoietic cells (magnification, ×10).

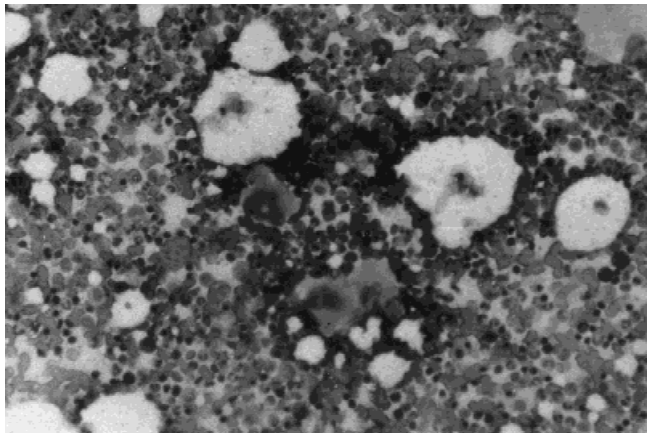

Fig. 3. Bone marrow imprint smear (thrombocytosis phase) shows an increased number of megakaryocytes and normal erythroid and myeloid series (magnification, ×100).

number of megakaryocytes (Fig. 3). The antiplatelet antibodies were measured by semiquantitative immunofluorescence technique [11]. It was absent during the thrombocytopenic as well as thrombocytosis phase on several occasions. Tests for rheumatoid factor and antinuclear antibodies were negative. The liver and renal functions were normal. The chest radiograph and ultrasonogram of the abdomen did not show any abnormalities. A diagnosis of cyclic AATP was made and the patient was started on danazol (10 mg/kg/d PO) in the month of October.

One more cycle of thrombocytopenia was observed and subsequently the range of variation in the platelet count decreased and the patient became asymptomatic and her menstrual cycle ceased. Danazol was given for a total period of 6 months and the minimum platelet count during treatment was above 200×10^9/l. After the cessation of therapy the cyclical variations in the platelet counts increased but the platelet counts at the nadir each cycle remained above 160×10^9/l and the patient continued to remain in clinical remission for the next 10 months (Fig. 1). Subsequently the patient has been lost to follow-up.

DISCUSSION

Cyclic hematopoietic disorders are rare and are characterized by regular predictable oscillations of one or more cellular elements of the blood. In a normal physiologic condition the circulating platelet counts are maintained within the normal range by a complex interplay between thrombopoietic stimulation and feedback inhibition. A defect in any one of these steps results in oscillation of the platelet counts (the cyclic thrombocytopenia) [12]. In the megakaryocytic type of cyclic thrombocytopenia, the bone marrow shows increased megakaryocytes during the period of thrombocytopenia. This variety is frequently seen in women and the nadir in platelet counts occurs in synchrony with the menstrual cycle and has been termed as ''menstrual cyclic thrombocytopenia.'' Antiplatelet antibodies are usually present and the platelet survival time is reduced [13–21]. Cyclic production of antiplatelet antibodies and/or modulation of platelet clearance by the reticulo-endothelial system due to normal variation in hormone levels have been suggested as the possible etiological factors for the production of menstrual cyclic thrombocytopenia [17–19]. In cyclic AATP the bone marrow shows fluctuations in the megakaryocyte counts, which is in synchrony with the changes in the platelet counts. Antiplatelet antibodies are usually absent and the platelet life-span is normal [1–6,9]. However, only Kimura et al. [7] have observed fluctuating levels of platelet-associated IgG (PA-IgG) in synchrony with the variations in platelet count in their male patient with cyclic AATP. The observation in the two types of cyclic thrombocytopenia has been corroborated by a study of Nagasawa et al. [22]. They evaluated the megakaryopoiesis in 10 patients with cyclic thrombocytopenia by measuring the number of colony-forming unit-megakaryocyte (CFU-Meg), megakaryocytes, and the mean cytoplasm area of megakaryocytes at different phases of the platelet cycle. In the megakaryocytic variety of cyclic thrombocytopenia the mean size of megakaryocytes did not change with the cyclic variations in platelet count, suggesting rapid platelet clearance to be responsible for the disorder. In contrast, in patients with amegakaryocytic variety, the values for CFU-Meg the megakaryocytic number and the cytoplasmic area fluctuated in synchrony with the platelet cycle indicating that there is a defect in megakaryopoiesis that occurs in cyclic pattern. The total absence of megakaryocytes in the bone biopsy during the phase of thrombocytopenia and increased megakaryocyte count during the thrombocytosis phase along with the absence of antiplatelet antibodies in our patients is in concordance with the findings in the previously reported cases of cyclic AATP [1–9].

The exact pathogenesis for suppression of megakaryopoiesis in cyclic AATP is not well understood and appears to be multifactorial. Hoffman et al. [9] detected the presence of an IgG antibody that blocked the action of granulocyte-macrophage colony-stimulating factor (GM-CSF) on the colony-forming unit-megakaryocyte (CFU-MK), in a female patient with cyclic AATP. The blocking effect appeared to be maximum during the period of thrombocytopenia and minimum when the platelet counts were normal. Dan et al. [5] observed that the cyclic fluctuation in the platelet counts was secondary to periodic failure of megakaryopoiesis at the stage of CFU-Meg and the peripheral mononuclear cells were responsible for suppressing the CFU-Meg. In contrast, Balduini et al. [6] found that in their patient, there was cyclic suppression not only of platelet production at the CFU-MK level but also suppression of multilineage erythroid and GM precursors and the defect possibly existed at the level of multilineage progenitors (CFU-Mix). Recently Kimura et al. [7] observed cyclic variation in the levels of various cytokines in a male patient with cyclic AATP. There was a positive correlation between IL-7, stem cell factor, and transforming growth factor B levels and the platelet counts. A negative correlation existed between the platelet counts and macrophage colony-stimulating factor and thrombopoietin levels. Similarly Kuyama et al. [10] observed that the levels of GM-CSF and IL-6 fluctuated in synchrony with the platelet count in their patient. Both of these observations suggest that a defect in cytokines mediated regulation of megakaryopoiesis may have an important role in the pathogenesis of this disorder. Estrogens have been observed to impair the hematopoiesis in animals [23]. Thrombocytopenic purpura following prolonged use of diethyl stilbesterol and other estrogenic hormone has been reported [24]. Estrogens also influence the expression of Fc receptors on the macrophages and the hormonal changes during the menstrual cycle may have a role in the production of cyclic AATP in women [20].

Treatment of patients with cyclic AATP is a major therapeutic challenge. Patients usually do not respond to prednisolone, intravenous Ig, splenectomy and the majority of reported cases have died due to life-threatening

hemorrhages [1–3,6]. Immunosuppressive drugs such as cyclosporin A and azathioprine have produced successful remission in two male patients with cyclic AATP [4,5]. Our patient had failed to respond to intravenous Ig and splenectomy but showed response to danazol. Danazol is a C-19 steroid derivative of 17-A ethinyl testosterone (ethisterone) and like natural sex steroid exerts a central inhibitory effect on the hypothalamic-pituitary function and produces a hypoestrogenic-hypoprogestational state. It also eliminates the ''midcycle'' of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) surge but does not alter the basal gonadotrophin levels in premenopausal women. In addition, it has an immunomodulatory action and also decreases the Fc receptor expression on the macrophages. Danazol has been found to be effective in the treatment of autoimmune thrombocytopenia and menstrual cyclic thrombocytopenia [21,25]. Rocha et al. [21] have successfully treated a female patient with menstrual cyclic thrombocytopenia with danazol and have suggested that its beneficial effect is probably mediated by the modulation of Fc receptor expression in the macrophages [21]. However, the mechanism of action of danazol in cyclic AATP is not clear and further studies are required for its understanding.

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